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EXAMINER	
SAOUD, CHRISTINE J	

ART UNIT	PAPER NUMBER
1647	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/901,938	Applicant(s) ECONS et al.
	Examiner Christine Saoud	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 4, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above, claim(s) *17-31, 34, 35, 39-42, and 44-83* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-16, 32, 33, 36-38, and 43* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group I, SEQ ID NO:1 in Paper No. 8 is acknowledged.

2. Claims 17-21, 25-31, 34-35, 39-42, 44-79, and 81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 8.

Additionally, upon the election of SEQ ID NO:1, claims 22-24, 80, 82-83 are also withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. These claims are limited to mutants, which do not read on the elected invention. Election was made without traverse in Paper No. 8.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

It is noted that at the time of the instant Office action, no IDS had been entered into the instant application.

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed (i.e. nucleic acids).

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see at least page 45, lines 4 and 19). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

6. The disclosure is objected to because of the following informalities: at page 10, line 12, there appears to be an amino acid sequence without a sequence identifier. 37 CFR 1.821(a)-(d) requires that any amino acid sequence of 4 or more amino acids be represented by sequence identifier in the Sequence Listing and referred to in the specification and/or claims by the SEQ ID NO:. Since this sequence is 4 amino acids long, it appears to require a sequence identifier.

Appropriate correction is required.

Claim Objections

7. Claims 1-16, 32-33, 36-38, and 43 are objected to because they include non-elected inventions. SEQ ID NO:1 was elected without traverse, and therefore, claims which encompass

SEQ ID NO:3, mutants, variants, and homologs are non-elected inventions and should be deleted from the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 5-16, 36-38, and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 recites "encoding a fibroblast growth factor-23 (FGF23)", "mutant", "variant", and "homolog". Claim 2 recites "wherein said isolated nucleic acid shares at least about 50% sequence identity" and claim 3 recites "wherein said isolated nucleic acid encodes a polypeptide having an amino acid sequence that shares at least about 40% sequence identity". However, the instant specification fails to provide a written description of that subject matter which is being claimed.

The specification states that mutants encompass changes in the nucleic acid sequence regardless of whether there is a change in the protein's structure or function and variants are peptides which are altered in the amino acid sequence but wherein the peptide has biological

activity of FGF-23 (see page 48 of the specification). The specification indicates that FGF23 is intended to have the amino acid sequence of SEQ ID NO:2, 4, or an amino acid sequence of about 40% sequence identity with these sequences and the specification intends homologs, which may be FGF23 from other species of mammals (see page 12 of the specification).

First, the recitation of "homolog" appears to be directed naturally occurring molecules isolated from other mammalian species. The structure of what would constitute a "homolog" cannot be predicted on the basis of the amino acid sequence of the human and mouse proteins because the instant specification fails to identify those portions which would be considered to be required for the biological activity of the encoded molecule or those portions which would be expected to be found in other species. The claims are directed to a species of nucleic acids, the structure of which cannot be determined or predicted from SEQ ID NO:1 and/or 3 and the specification does not evidence isolation or conception of the structure of a homolog, variant or mutant, other than the specifically identified mutations at positions 176 and 179. Therefore, the specification does not provide an adequate written description of a homolog, mutant or variant, other than the disclosed embodiments identified above, and thus the claimed invention, to the extent that it reads upon homolog, mutant and variant, was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

With the exception of very particular amino acid and nucleic acid sequences which are disclosed in the instant application, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotide molecules and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific molecular structure is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) The instant claims are directed to a structure, which could be made, but for which, there is no written description. As in Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class because the specification provided only the bovine sequence. In the instant situation, the specification only provides the structure for the human and

mouse, including 3 point mutations, but fails to provide a description of the "broad class" of mutants, variants and homologs, regardless of whether they could be made or isolated.

10. Claims 1-3, 5-16, 36-38, and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims include embodiments of nucleic acid having at least 50% sequence identity to SEQ ID NO:1 or 3, as well as encoding a polypeptide having an amino acid sequence at least 40% identical to SEQ ID NO:2 or 4. The instant specification fails to describe molecules which meet these limitations of the claims. First, the instant specification teaches two examples of a polynucleotide (SEQ ID NO:1 and 3) as well as 3 naturally occurring point mutations, but fails to teach the degree of variation which is claimed (i.e. 50% difference from the disclosed nucleic acid or 60% difference from the disclosed amino acid sequence). In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant has possession of nucleic acid molecules with the sequence of SEQ ID NO:1 and 3, as well as 3 point mutations in these molecules. The subject matter which is claimed is described above. First, a determination of the level of predictability in the art must be made in that whether the level of skill in the art leads to a

predictability of structure; and/or whether teachings in the application or prior art lead to a predictability of structure. The claims are directed to nucleic acid molecules which have sequence identity to SEQ ID NO:1 or 3, as well as to molecules which encode protein which have sequence identity to SEQ ID NO:2 or 4, as well as to mutants, variants and homologs. First, the claims are not limited to any particular polynucleotide, in that the claims are also directed to variant and mutant forms thereof. The specification only describes two molecules, as well as 3 point mutations, and fails to teach or describe any molecules which meet the full scope of the percent identity structural limitations of the claims. The breadth of the claims is such that the claims encompass molecules from other species, related molecules, mutants and variants which have yet to be described. There is a lack of guidance or teaching regarding structure and function of the molecules because there are only two examples provided in the specification and because there is no guidance found in the prior art for this specific molecule.

Next in making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, each claimed species and genus must be evaluated to determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention at the time the application was filed. With this regard, the instant application fails to provide a written description of the species or the genus which are encompassed by the instant claims except for the molecules of SEQ ID NO:1 and 3. The specification does not provide a complete structure of those molecules which have at least 50% sequence identity to SEQ ID NO:1 or 3, encode polypeptides which have at least 40%

sequence identity to SEQ ID NO:2 or 4, to variants other than those 3 point mutations identified in the specification, to mutants or to homologs. The claims also fail to recite other relevant identifying characteristics (physical and/or chemical and/or functional characteristics coupled with a known or disclosed correlation between function and structure) sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. The specification fails to provide a representative number of species for the claimed genus because the specification teaches only two embodiments, one from human and one from mouse, and only 3 variants (point mutations). Therefore, the claims are directed subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

11. Claims 1-16, 32-33, 36-38, and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

12. Claim rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling an isolated nucleic acid molecule of SEQ ID NO:1, including mutations of R176Q, R179Q and R179W, does not reasonably provide enablement for mutants, variants, homologs, fragments and nucleic acids having at least about 50% sequence identity or nucleic acids encoding

proteins having at least 40% sequence identity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification describes a nucleic acid molecule of SEQ ID NO:1 which is associated with ADHR (autosomal dominant hypophosphatemic rickets), as well as 3 mutations (R176Q, R179Q and R179W) which appear to be causative for ADHR. Therefore, the nucleic acid of SEQ ID NO:1, as well as the nucleic acids associated with the disclosed mutations would be useful in a diagnostic application for detecting ADHR. However, the instant claims encompass generically mutants, variants, homologs, fragments, and molecules which share % identity to the disclosed molecules. The instant specification fails to enable one of ordinary skill in the art to make and use such molecules in a real world context; i.e. for detecting ADHR. The instant specification provides no guidance as how to modify the disclosed nucleic acids and obtain a nucleic acid which has a biological activity of the native molecule disclosed or which could be used as a diagnostic for ADHR. The specification provides no guidance as to which structural elements of the native molecule are critical to the biological activity. Without this type of guidance, the skilled artisan does not have a reasonable expectation of mutating the nucleic acid of SEQ ID NO:1 and obtaining a functional and useful nucleic acid. One may argue screening for bioactivity could be done, however, this is basically a "wish to know" and the standard for an enabling disclosure is not one of making and testing. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function

in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them, then the instant application does not support the breadth of the claims.

A review of *In re Wands* clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the enablement of an invention. The claims encompass a limitless number of embodiments because they recite no structural limitations on the claimed molecules (i.e. mutant and variant could encompass limitless variation). The specification provides no guidance as to amino acid positions and/or regions which would provide biological activity (factor 2) and provides no examples of any molecules which differ by as much as 50% nucleic acid sequence identity or 60% amino acid sequence identity, and only describe 3 naturally occurring mutations (factor 3). The claims encompass molecules wherein 60% of the amino acid sequence is missing, however, one of ordinary skill in the art would not reasonably expect that a molecule that meets this limitation of the claims to be sufficient for biological activity, such as receptor binding or activation. The claims are exceedingly broad because they encompass mutants, variants, homologs and fragments, which means that not a single amino acid need be the same, but only similar (factor 8). In addition,

although the skill in the art is known to be high (factor 6), the results of mutating amino acids to produce a function protein is highly unpredictable (factors 4, 5 and 7). Therefore, in light of this analysis, one would reasonably conclude that the breadth of the instant claims is not commensurate in scope with the specification, absent evidence to the contrary.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-4, 7, 12, and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "fibroblast growth factor-23 (FGF23)", however, the metes and bounds of what this encompasses are not clear. The art acknowledges that many proteins may go by different names as well as some names which can signify many different proteins. Therefore, the mere recitation of a name places no material limitations on what is being claimed. In the art of fibroblast growth factors, the newest member is given the next highest number. However, as in any art, there are new protein members being discovered daily, therefore, Applicant's "FGF23" may be someone else's "FGF25". Therefore, the instant claim is indefinite.

Claim 2 recites "a nucleic acid sequence of at least one of SEQ ID NO:1 and SEQ ID NO:3" and claim 3 recites "an amino acid sequence of at least one of SEQ ID NO:2 and SEQ ID NO:4". The use of the articles "a" and "an" in conjunction with "sequence" appears to imply that

there may be more than one sequence associated with the Sequence identifiers. This is a reasonable interpretation of the claims since a number of nucleic acids have been found to be alternatively spliced, as well as proteins which may have different proteolytic processing depending on tissue expression. Therefore, these claims are indefinite because it is not clear which sequence is intended by the claims. This ground of rejection could be obviated by the use of "the" in place of "a" and "an".

Claim 2 recites "at least about 50% sequence identity"; however, this recitation is indefinite because the lower limit of what is intended is not clearly defined. "At least" means that the molecule will have 50% or more sequence identity, which is definite. However, the inclusion of "about" does not provide a lower limit, making the claims indefinite (i.e. is 45% encompassed, 48%, 40%, etc.).

Claim 4 recites "[a]n isolated nucleic acid included in DSMZ Deposit No. DSM 13530". However, the recitation of "included" is unclear and indefinite as to which nucleic acid is encompassed by the claim. The specification at page 40, lines 21-23 states "deposit of nucleic acid including FGF23 DNA, was made with the German collection of Microorganisms and Cell Cultures (DSMZ)". Therefore, it would appear that there is other DNA present in the deposit by the presence of the recitation of "including". In view of this, it is not clear what is being claimed from the Deposit and the metes and bounds of the claim cannot be determined. If the intended nucleic acid encodes a protein with a particular amino acid sequence, this information could be

added to the claim as a limitation to distinguish from other nucleic acid which may be contained in the Deposit.

Claims 7 and 15 recite "comprising a nucleic acid specifying a promoter/regulatory sequence". The nature of the term "specifying" is not clear. Since promoter/regulatory sequence associated with nucleic acids are implied to be nucleic acid sequences as well, it would appear that the recitation of "nucleic acid specifying" is redundant and confusing. "Specifying" means to state explicitly, and it is not clear what limitation this places on the promoter/regulatory sequence. As this recitation does not seem to be art recognized, the claims would appear to be more clear if this language were simply omitted (i.e. said nucleic acid further comprising a promoter/regulatory sequence operably linked thereto).

Claims 12 and 43 are directed to complementary nucleic acid molecules, "said complementary nucleic acid being in an antisense orientation". The recitation of "being in an antisense orientation" is redundant to the claim directed to the complementary molecule because complementary molecules are already in an antisense orientation by definition of "complementary". Therefore, it is not clear what is intended by the limitation that "said complementary nucleic acid being in an antisense orientation". Would this mean "antisense" of the complement, which would be "sense" or is this merely redundant for the reasons provided above? It is suggested that the phrase "said complementary nucleic acid being in an antisense orientation" be removed from the claims as it appears to be redundant. The specification states that "antisense" refers to "a sequence which is substantially homologous to the non-coding

strand" (see page 43, lines 25-26). This definition is replete with indefinite terms and the metes and bounds of "substantially homologous" cannot be determined. "Substantially" is a relative term of degree without an indication of what would be considered "substantial" and "homologous" means similar or corresponding in position, value, structure or function. Therefore, both terms are vague and indefinite for defining "antisense", and such a definition would be repugnant to the art.

Claim 43 recites "an isolated protein having the biological activity of fibroblast growth factor-23", however, no biological activity is provided in the claim. Without an indication of which biological activity is intended by the claim, the metes and bounds of "the biological activity" cannot be determined and the claim is indefinite.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Mahmood et al. (Develop. 121: 1399-1410, 1995).

Mahmood et al. teach a polypeptide which comprises at least a single nucleotide in common with SEQ ID NO:1. This would appear to comprise a fragment as required by the claim

as there is no size limitation on the "fragment". Therefore, the claim is anticipated by the prior art.

Conclusion

17. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The Examiner can normally be reached on Monday to Thursday from 8AM to 2PM. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §§ 1.6(d) and 1.8). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternate number. Official papers filed After Final rejection filed by fax should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud